BI-1942: A Chemical Probe for CMA1

Version 1.0 (20th June 2021)

Web link for more details: https://www.sgc-ffm.uni-frankfurt.de/#!specificprobeoverview/BI-1942

Overview

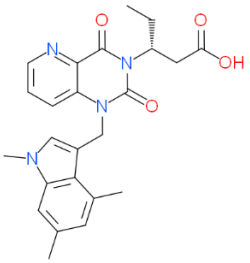
CMA1 (chymase) is a chymotrypsin-like serine protease stored in a latent form in the secretory granules of mast cells. Upon stimulation the active form contributes to the activation of TGF-ß, matrix metalloproteases and cytokines. Cardiac chymase is involved in the formation of angiotensin II and plays a role in activating TGF-ß1 and IL-1ß, generating endothelin, altering apolipoprotein metabolism and degrading the extracellular matrix. It has been linked to heart failure.

Summary

Chemical Probe Name	BI-1942
Negative control compound	NA
Target(s) (synonyms)	CMA1 (chymase 1)
Recommended *in vitro* assay concentration	Use at concentration up to 1µM.
Suitability for *in* vivo use and recommended dose	Not for use in vivo
Publications	None at time of writing
Orthogonal chemical probes	
In vitro assay(s) used to characterise	Inhibition of CMA1
Cellular assay(s) for target-engagement	Angiotensin II formation by CMA1 in human plasma

Chemical Probe & Negative Control Structures and Use

BI-1942 Chemical Probe



Negative Control

NA

SMILES:
CC[C@H](CC(O)=O)N1C(c2c(cccn2)N(Cc2cn(C)c3cc(C)cc(C)c23)C1=O)=O
InChiKey: PCJVXTDIDUMIRR-QGZVFWFLSA-N
Molecular weight: 434.2
Storage: As a dry powder or as DMSO stock solutions (10 mM) at -20 °C. DMSO stocks beyond 3-6 months or 2 freeze/thaw cycles should be tested for activity before use
Dissolution: Soluble in DMSO up to 10 mM; use only 1 freeze/thaw cycle per aliquot

Chemical Probe Profile

In vitro Potency & Selectivity:

BI-1942 shows potent inhibition of human CMA1 (IC_{50} = 0.4 nM). Only one off-target was found in a Eurofins protease panel (Eurofins (35) at 10 µM): CTSG (cathepsin G) with IC_{50} = 110 nM. The Eurofins SafetyScreen (44) at 10 µM is clean.

Potency in Cells and Cellular Target Engagement:

Angiotensin II formation by CMA1 in human plasma: IC_{50} = 198 nM